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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,712	08/25/2000	Peter Nawroth	8484-075-999	7074

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Pennie & Edmonds
1155 Avenue Of The Americas
New York, NY 10036-2711

EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/423,712	NAWROTH ET AL.	
	Examiner	Art Unit	
	Janice Li	1632	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-17 and 20-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-17 and 20-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 August 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group II (claims 7-17, 20, and 21) in Paper No. 10 is acknowledged. Claims 1-6 have been canceled, claims 7, 10-14, 17, and 18 have been amended. Claims 20-32 are newly added. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)), thus, claims 18 and 19 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10.

Claims 7-17, and 20-32 are under current examination.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because it does not identify the citizenship of each inventor, and the post office addresses are incomplete missing country and the ZIP Code designation for some of the inventors.

Specification

The drawings are objected to under 37 CFR 1.83(a) because they fail to show the proper correspondence with the brief description of the drawings in the specification. Figures 2 and 3 are not present in the specification. Figures 1, 2A, and 3A contain three panels, however, the brief description does not describe each of these panels.

Appropriate correction is required.

Claim Objections

Claim 22 is objected to because of the following informalities: claim 22 is the duplicate of claim 20. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-17, and 20-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for promoting skin wound healing in a diabetic mouse model by surface administering a nucleic acid expressing the tissue factor, does not reasonably provide enablement for enhancing blood vessel formation in any location of the subject, or for treatment of diseases in human by any routes. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

Claim 1 recites "a method of modulating blood vessel formation in a subject in need", claims 30-32 recite "wherein the said subject in need is afflicted with diabetes mellitus, vasculitis..." and other disorders associated with impaired blood vessel formation. These claims clearly or implicitly state the intended use of the methods. With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph entails the determination of what the claims recite and what the claims mean as a whole. When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest reasonable interpretation of the claimed invention properly encompasses gene therapy for impaired wound healing-associated diseases, therefore, the claims will be evaluated by that standard.

The invention being gene therapy, the state of the art is not well developed and is highly unpredictable. *Verma et al* (Nat. 1997 Sep; 389:239-242) state that out of the more than 200 clinical trials for gene therapy currently underway, no single outcome can

be pointed to as a success story (page 239, col. 1). In view of the state of the art in gene therapy for human, *Levine et al* (Mole Med Today 1999 Apr; 5:165-171) teach "A CAVEAT WITH ALL OF THESE STUDIES IS THAT THE IMMUNE RESPONSE IS ENORMOUSLY COMPLEX AND THAT SUBTLE DIFFERENCES BETWEEN SPECIES AND THE EXPERIMENTAL MODEL USED CAN RESULT IN DRAMATICALLY DIFFERENT RESULTS. FOR EXAMPLE, THERAPIES THAT PREVENT DIABETES IN RODENT MODELS OF DIABETES HAVE NOT BEEN EFFICACIOUS IN HUMANS". "THERAPIES THAT PREVENT DIABETES IN RODENT MODELS OF DIABETES HAVE NOT BEEN EFFICACIOUS IN HUMANS" (page 167, left Col.).

In view of gene therapy for treating wound healing impairment and for blood vessel formation, the state of the art is not well developed and is highly unpredictable. Although TF is known in the art for its blood clotting effect (US 6,093,399) and particularly coagulation of tumor vasculature causing tumor regression, no art of record teaches using TF for promoting blood vessel formation and enhancing wound healing. The recited conditions, such as human diabetes mellitus, vasculitis, arterial conclusive disease, infected ulcer, Crohn's disease, and ulcerative colitis, have distinct and complicated etiologies and mechanisms that lead to impaired wound healing, whether a locally applied expression vector could really improve the wound healing in such patients is unknown; and how to deliver said vector to the targeting tissue other than skin surface is also problematic. Furthermore, the recited tissue factor has multiple functions, particularly blood clotting and vessel coagulating functions. *McDonald et al* (US 6,120,799) teach the presence of tissue factor in a tissue with blood vessels would result in the formation of blood clots prevent the flow of nutrients and oxygen to the remainder of the vessel, resulting in the death of the vessel and the surrounding tissue

(column 22, lines 1-7). From above teachings, the locally applied nucleic acids expressing TF could either promote the blood vessel formation or resulting in death of a vessel and surrounding tissue, thus, the outcome of using TF in a patient would be highly unpredictable given the nature of the TF having such distinct and paradoxical effects.

Thus, it is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential of gene therapy, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. Although the instant specification provides a brief review of a potential therapeutic use of the claimed method and data from a mouse study. It fails to teach enhancing blood vessel formation or wound healing in locations other than skin wound, and any therapeutic regime and effect in patients of any disease. In summary, the teachings and guidance present in the specification, as a whole, represent an initial investigation into the feasibility of the development of a useful means for executing gene therapy for wound healing and blood vessel formation, which awaits further development to the practical level. In view of such, undue experimentation is required for the skilled artisan intending to practice the invention.

Claims 20-22 recite a method comprising inducing local expression of a tissue factor nucleic acid in said subject. However, the claims or specification do not set forth steps for practice the invention other than skin surface administering a nucleic acid

expressing TF. One skilled in the art would not appreciate the scope of the invention, what these claims intend to embrace.

Therefore, in view of the limited guidance, the lack of predictability of the art, the nature and breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-17, and 20-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7-12 are vague and indefinite because they are incomplete. The claims provide for a method of modulating blood vessel formation, however, the claims do not recite a positive step or conclusion, which clearly relates back to the preamble, and it is unclear how mere administration of TF relates to modulating blood vessel formation.

Claim 7 is vague and indefinite because the claim recitation "a fragment thereof". The specification fails to teach the lower limit for the nucleic acid fragment encoding the tissue factor, which maintains the function of the tissue factor.

Claims 13-17, 20-32 are vague and indefinite. The method provides for inducing local expression of tissue factor nucleic acid in said subject, however, it does not recite positive steps of the method. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and

circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 7-10, 13-17, and 20-25 are rejected under 35 U.S.C. 102(e) as being anticipated by *McDonald et al* (US 6,120,799).

These claims are drawn to a method of modulating blood vessel formation in a subject comprising locally administering a functional tissue factor to a subject in need, wherein said TF or a fragment thereof is administered in the form of an expressible nucleic acid, wherein the nucleic acid is expressed transiently, and controlled by a constitutive or inducible promoter, wherein said tissue factor is present in a liposome, and combined with further factors promoting the formation of blood vessels, preferably VEGF.

McDonald et al teach a method selectively targeting vascular endothelial cells by delivering cationic lipid and DNA complex to vascular endothelial cells in a subject,

wherein the complexes may comprise nucleotide constructs having promoters which are selectively and exclusively activated in the environment of a vascular endothelial cell (abstract), wherein the construct could encode a human tissue factor (column 22, lines 14-15). *McDonald et al* go on to teach that the invention would result in the formation of blood clots prevent the flow of nutrients and oxygen to the remainder of the vessel, resulting in the death of the vessel (down-regulation or negative modulation) and the surrounding tissue. They also teach that the construct could encompass VEGF as angiogenesis mediating factor (column 19, line 62). Thus, *McDonald et al* anticipate the instant claims.

Note in this rejection and the rejection that follows, the claim recitation of claim 21 "a method for enhancing wound healing" has not been given patentable weight because the recitations occur in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7-17, and 20-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over *McDonald et al* (US 6,120,799) as applied to claims 7-10, 13-17, and 20-25 above, and further in view of *Dubensky, Jr. et al* (J Virology 1996 Jan;70:508-19).

Claims 11, 12, 26, and 27 are further directed to a Sindbis virus replicon vector as the preferred DNA construct and a CMV or SV40 promoter. *McDonald et al* and *Nakagawa et al* do not teach such vector construct.

Dubensky, Jr. et al teach Sindbis virus DNA-based expression vectors for *in vitro* and *in vivo* gene transfer. They teach that these vectors are desirable alternative to other virus-derived vector systems being developed, because they could express potentially high-levels of heterologous protein per cell, have a broad host range, and infect nondividing cells (Introduction). They teach that such vector comprises a CMV or SV40 promoter (left column, 3rd paragraph in page 509).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *McDonald et al*, by simply substituting the plasmid vector with a Sindbis virus replicon vector as taught by *Dubensky, Jr. et al*. The ordinary skilled artisan would have been motivated to modify the claimed invention for enhanced gene delivery and expression with a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 7-10, 13-17, 20-25, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over *McDonald et al* (US 6,120,799) as applied to claims 7-10, 13-17, and 20-25 above, and further in view of *Sanford et al* (US 5,100,792).

Claim 28 is further directed to using a gold particle as a carrier for administering the nucleic acids. *McDonald et al and Nakagawa et al* do not teach the gold particle delivery.

Sanford et al teach using inert or biologically active particles to deliver nucleic acids into living cells, such as gold particle (column 6, line 45), such practice has become routine in the field of gene transfer.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *McDonald et al* by simply including the gold particle in the delivery complex as taught by *Sanford et al*. The ordinary skilled artisan would have been motivated to modify the claimed invention for enhanced gene delivery with a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed. Claim 29 appears to be free of the cited prior art of record, however, it is subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p:m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Crouch can be reached on 703-308-1126. The fax numbers for the organization where this application or proceeding is assigned are 703-308-8724 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
December 28, 2001

JAMES KETTER
PRIMARY EXAMINER